Extramural papers of the month

By Nancy Lamontagne

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Epigenetic changes associated with pancreatic cancer might lead to early detection

In work funded in part by the NIEHS, researchers identified epigenetic modifications in BNC1 and ADAMTS1 genes that were detectable in people with early-stage pancreatic cancer, but not in cancer-free people. The findings from this small preliminary study point to the possibility of a blood test that might detect early-stage pancreatic cancer. Pancreatic cancer is almost always fatal, because it isn't usually discovered until it has spread.

The researchers used methylation on beads technology, a recently developed approach that uses nanotechnology to capture and analyze very small amounts of DNA. Using this method, they detected methylation changes in DNA circulating in 42 serum samples from patients with pancreatic cancer. For the BNC1 gene promoter, the researchers achieved a sensitivity of 79 percent and specificity of 89 percent, and for the ADAMTS1 gene, the sensitivity was 48 percent and specificity 92 percent. When using both markers, the approach achieved an overall sensitivity of 81 percent (95 percent confidence interval [CI], 69-93 percent) and specificity of 85 percent (95 percent CI, 71-99 percent).

The researchers say that, although larger studies are needed, their findings strongly suggest that BNC1 and ADAMTS1 promoter methylation could be used as biomarkers for identifying individuals at risk for pancreatic cancer.

Citation: Yi JM, Guzzetta AA, Bailey VJ, Downing SR, Van Neste L, Chiappinelli KB, Keeley BP, Stark A, Herrera A, Wolfgang C, Pappou EP, Iacobuzio-Donahue CA, Goggins MG, Herman JG, Wang TH, Baylin SB, Ahuja N.
(http://www.ncbi.nlm.nih.gov/pubmed/24088737)
2013. Novel methylation biomarker panel for the early detection of pancreatic cancer. Clin Cancer Res 19(23):6544-6555.

Phthalate exposure linked to preterm birth

NIEHS-supported research has found that, depending on the phthalate examined, women with the highest levels of exposure during pregnancy had 2-5 times the odds of preterm birth, compared to women with the lowest exposure. The findings point to phthalate exposure as a potentially preventable contributing factor to premature birth.

Using a nested case control study design, the researchers examined associations between average levels of phthalate exposure during pregnancy and preterm birth in 130 mothers who had delivered prior to 37 weeks of completed gestation. The study also included 352 control mothers who delivered at or after 37 weeks. To determine overall phthalate exposure, the researchers used multiple urine samples during pregnancy. They found that preterm birth showed the strongest dose-dependent associations with maternal levels of the two di-2-ethylhexyl phthalate (DEHP) metabolites, mono-(2-ethyl)-hexyl phthalate (MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and the summed levels of all the DEHP metabolites.

The researchers also analyzed a subset of 57 mothers with preterm deliveries preceded by spontaneous preterm labor or preterm premature rupture of the membranes. When this group was examined alone, the odds ratios increased for all the phthalate metabolites. This finding indicates a stronger association between phthalate exposure and spontaneous preterm birth than the association with all preterm births.

Phthalate exposure can occur from food, plastics, and personal care products, such as deodorants and lotions. The researchers caution that, before implementing interventions aimed at decreasing phthalate exposure, more studies are needed to confirm these findings, to examine the sources of the phthalates, and to better understand the mechanisms involved.

Citation: Ferguson KK, McElrath TF, Meeker JD.
(http://www.ncbi.nlm.nih.gov/pubmed/24247736)
2013. Environmental phthalate exposure and preterm birth. JAMA Pediatr; doi:10.1001/jamapediatrics.2013.3699 [Online 18 November 2013]. (Story)

A 3-D map of chromatin interactions

An NIEHS grantee and colleagues generated a high-resolution map of three-dimensional (3-D) chromatin interactions in human cells. The map suggests that the looping structure of chromatin is relatively stable, once established in a cell type.

DNA contains areas known as cis-regulatory sequences where transcription factors can bind to regulate gene expression. The 3-D loops of chromatin help control gene expression, by bringing cis-regulatory DNA sequences close to their target genes. Although scientists have identified a large number of cis-regulatory sequences in the human genome, many of the target genes for these sequences are unknown. To identify these target genes, the researchers mapped the 3-D interactions of cis-regulatory sequences in human fibroblast cells, using a genome-wide chromosome conformation capture analysis method.

The researchers determined more than 1 million long-range chromatin interactions at a resolution of 5-20 kilobases. One of their findings was that DNA sequences, activating gene expression after treatment of cells with the tumor necrosis factor alpha, are already in contact with their target promoters before signaling.

This unexpected discovery suggests that enhancer-promoter interactions form before signaling and change little when activated during transcription. Thus, the looping structure of chromatin is likely cell-type specific, and could influence the selection or activation of target genes by a ubiquitous transcription activator.

Citation: Jin F, Li Y, Dixon JR, Selvaraj S, Ye Z, Lee AY, Yen CA, Schmitt AD, Espinoza CA, Ren B. *(http://www.ncbi.nlm.nih.gov/pubmed/24141950)*
2013. A high-resolution map of the three-dimensional chromatin interactome in human cells. Nature 503(7475):290-294.

Girls are reaching puberty earlier

Research that is part of the NIEHS Breast Cancer and the Environment Research Program, a cohort of more than 1200 girls, found that breast development is occurring at an earlier age, and that earlier development was strongly associated with greater body mass index (BMI). Earlier than average maturation is a risk factor for obesity and hypertension, as well as breast, ovarian, and endometrial cancer.

From 2004 to 2011, the researchers followed girls in the San Francisco Bay Area, Greater Cincinnati, and New York City who were 6-8 years old when enrolled in the study. At regular intervals, trained and certified staff used Tanner staging to assess sexual maturity. They found that the age at onset of breast development (stage 2) varied by race/ethnicity, BMI at baseline, and geographical site. For African-American, Hispanic, white non-Hispanic, and Asian participants, the median age at onset of breast stage 2 was 8.8, 9.3, 9.7, and 9.7 years, respectively. Girls with BMIs greater than the 85th percentile reached breast stage 2 at younger ages.

Compared to data from studies conducted in the 1990s, white non-Hispanic girls are now maturing at younger ages, while the maturation age for African-American girls is similar to that found in the earlier studies.

Citation: Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Hiatt RA, Kushi LH, Wolff MS. *(http://www.ncbi.nlm.nih.gov/pubmed/24190685)*
2013. Onset of breast development in a longitudinal cohort. Pediatrics 132(6):1019-1027.

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